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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/29/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/472,691	HERMISTON ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/28/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *2/28/03* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-15 are pending.

Applicants' traversal filed on 2/2/8/03 is acknowledged and considered.

Claim Objections

Applicants' arguments, see paper no. 18, filed 8/28/02, with respect to the objection have been fully considered and are persuasive. The objection of claim 11 has been withdrawn.

Claims 3 and 4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The p19 gene and 55K gene and pIX gene were already deleted according to claim 2, from which claims 3 and 4 depend.

Claim 15 is objected to because of the following informalities: the term "gene(s)" is improper. Suggest removing "(s)" from the term. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Applicants' arguments, see paper no. 18, filed 2/28/03, with respect to the enablement rejection have been fully considered and are persuasive. The rejection of claims 10 and 11 under 112 first paragraph enablement has been withdrawn.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 4, 6, 7, 9, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure, which is not enabling. Operably linking a heterologous gene to the E1b promoter is considered critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The claimed invention encompasses "a recombinant adenoviral vector comprising a deletion of at least one E1b region gene (p19, 55K, and/or pIX) but retaining the E1b promoter and substituting for said E1b region gene a heterologous gene that has a similar temporal expression pattern of the deleted E1b region gene...preferably driven by the endogenous E1b promoter" (page 3, lines 15-30). It appears from the specification that operably linking a heterologous gene to the E1b promoter is considered critical or essential to practice the claimed invention. However, the adenovirus pIX gene is technically not considered an E1b region gene. The art of record teaches that pIX gene has its own promoter (Babiss et al. Journal of Virology 65: 598-605, 1991). Thus, if only the pIX coding sequence was replaced with the heterologous gene then the pIX promoter would still be present and the heterologous gene would not be operably linked to the E1b promoter. In view of *In re Mayhew*, the claims are not enabled by the disclosure.

Applicant's arguments with respect to claims 1 and claims dependent therefrom have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments, see paper no. 18, filed 2/28/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 2, 3, 4, 5, 6, and 11 has been withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2, 3, 4, 6, 7, 8, 9, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "a heterologous gene that has a similar temporal expression pattern of the deleted E1b region gene" in Claims 1, 2, 3, 4, 6, 7, 9, 10, and 11 is a relative term which renders the claims indefinite. The term "a heterologous gene that has a similar temporal expression pattern of the deleted E1b region gene" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification and the claims do not define the metes and bound of the term because it is unclear if the "temporal expression" limitation applies to the endogenous gene expression or the expression in the vector.

Suggest replacing "that" on line 3 with -- such that the heterologous gene --.

Applicants' arguments with respect to claim 1 and claims dependent therefrom have been considered but are moot in view of the new ground(s) of rejection.

Claims 2, 3, and 4 recite the limitation "said E1b region genes". There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites "E1b region gene".

Applicants' arguments with respect to claims 2, 3, 4 have been considered but are moot in view of the new ground(s) of rejection.

Claims 7, 8, 9, and 10 recite the limitation "said adenoviral vectors". There is insufficient antecedent basis for this limitation in the claim. Claims 1, 5, 6, or 15 recite "adenoviral vector".

Applicants' arguments with respect to claims 7-10 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6-7, 9-11, and 14-15 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bischoff (US Patent No. 6,080,578). Bischoff teaches mutant adenoviruses with a replication competent phenotype in neoplastic cells (abstract). Bischoff further teaches that the preferential killing of the neoplastic cells resulted either directly or by the expression of a cytotoxic gene in cells (abstract). Furthermore, Bischoff teaches recombinant adenovirus constructs comprise a mutation in the E1a and/or E1b 55 protein (column 4, lines 32-54). A gene is operably linked to an early region (e.g. E2, E1a, E1b) enhancer/promoter, or an early gene promoter. In addition, Bischoff also taught the construction of plasmids comprising several E1B deletions and deposited at the ATCC depository (column 11, line 24- column 14, line 18, claims 4-6, and columns 25 and 26). Bischoff also teaches the efficacy of ONYX-015 (note that ONYX-015 does not make detectable 55kD) alone and in combination with chemotherapy in a research tumor animal model (column 22, line 55 - column 23).

Applicants' arguments filed 2/28/03 have been fully considered but they are not persuasive because the claims read on a recombinant adenoviral vector taught by Bischoff comprising a deletion of at least one E1b region gene, but retaining the E1b promoter operably linking to an anti-tumor gene and using the adenoviral vector to treat a tumor in an animal. More specifically, Bischoff teaches an adenoviral vector comprising a deletion in the E1a and/or E1b gene region especially E1b 55 protein and operably linking HSV tk gene to E1b promoter (column 4, lines 31-55). Applicants admit that Bischoff teaches deleting one E1b region gene (55K) in an adenoviral vector (see page 5).

In addition, applicants citing pages 13 and 15 of paper no. 7 for support of their argument is not found persuasive because pages 13 and 15 are directed to a 103 rejection and not the 102(e) rejection.

Claim Rejections - 35 USC § 103

Applicants' arguments, see paper no. 18, filed 2/28/03, with respect to the 103(a) rejection have been fully considered and are persuasive. The rejection of claims 1, 2, 4, 7, 14, and 15 as being unpatentable over Bischoff taken with Amalfitano has been withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff (US Patent No. 6,080,578) taken with Garcia-Sanchez et al. (Blood, Vol. 92, 1998, pp. 672-682). Bischoff teaches mutant adenoviruses with a replication competent phenotype in neoplastic cells (abstract). Bischoff further teaches that the preferential killing of the neoplastic cells resulted either directly or by the expression of a cytotoxic gene in cells (abstract). Furthermore, Bischoff teaches recombinant adenovirus constructs comprise a mutation in the E1a and/or E1b 55 protein (column 4, lines 32-54). A gene is operably linked to an early region (e.g. E2, E1a, E1b) enhancer/promoter, or an early gene promoter. In addition, Bischoff also taught the construction of plasmids comprising several E1B deletions and deposited at the ATCC depository (column 11, line 24- column 14, line 18, claims 4-6, and columns 25 and 26). Bischoff also teaches the efficacy of ONYX-015 (note that ONYX-015 does not make detectable 55kD) alone and in combination with chemotherapy in a research tumor animal model (column 22, line 55 - column 23). However, Bischoff does not specifically teach using an anti-tumor gene, wherein the gene is cytosine deaminase (CD) in the adenoviral vector.

However, at the time the invention was made, Garcia Sanchez teaches production of adenoviral vector comprising a cytosine deaminase (CD) used for killing cancer cells (abstract).

CD converts the antibiotic pro-drug 5-fluorocytosine into the cytotoxic chemotherapeutic agent 5-fluorouracil.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to insert a CD gene instead of thymidine kinase gene into the recombinant adenoviral vector taught by Bischoff. One of ordinary skill in the art would have been motivated to insert any anti-tumor gene (e.g. CD) in the recombinant adenoviral vector because Bischoff teaches that any cytotoxic gene could be use to treat tumor cells in an animal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicants' arguments filed 2/28/03 have been fully considered but they are not persuasive. Bischoff teaches an adenoviral vector comprising a deletion in the E1a and/or E1b gene region especially E1b 55 protein and operably linking HSV tk gene (anti-tumor gene) to E1b promoter (column 4, lines 31-55). Garcia Sanchez teaches using CD (anti-tumor gene) in an adenoviral vector to kill cancer cells. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In view of the totality of the prior art, one of ordinary skill in the art would have been motivated to use an anti-tumor gene selected form either CD or HSV-tk in the adenoviral vector taught by Bischoff to kill cancer cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER